Drugs in Pregnancy

Their Effects on the Fetus and Newborn

DOUGLAS H. SANDBERG, *M.D.*, Los Angeles

• **In considering drug therapy for pregnant women, it must be borne in mind that almost all chemical compounds in use as therapeutic agents pass from the maternal to the fetal circulation through the placenta. These drugs can produce a wide range of harmful effects on the fetus and neonatal infant. The effects of some substances for which we have data reflecting a deleterious effect are listed.**

It is suggested that in the future more caution be exercised in using drugs during pregnancy and that in histories, both obstetrical and pediatric, any therapy given to the mother during gestation be recorded in detail.

IT HAS BEEN RECOGNIZED for a long time that drugs given to a pregnant woman may pass through the placenta into the fetal circulation. It is only comparatively recently that the significance of this phenomenon has been recognized, the stimulus to studies of the question having come from the increasing evidence of fetal problems traced to the use of drugs during pregnancy. Although information on this subject is meager, studies are now rapidly appearing. The present communication is a brief summary of some of the practically useful data on the placental transfer of drugs.

The old concept of the placenta as a "barrier" is misleading. It is better characterized as a filter. At any rate, we now know that almost all drugs pass the placenta and appear in the fetal circulation, although often the concentration of the drug is a great deal higher on one side of the placenta than on the other. The placenta is actively involved in the transport of certain substances—sodium, for example—which may explain the gradient of concentration found. Substances of high molecular weight, like proteins, pass only slowly and in small amounts through the placenta. There is some question as to whether thyrotropic hormone and parahormone pass at all, and curare given to the mother does not appear in the fetal circulation.

Differences in placental passage of drugs during normal as compared with complicated pregnancy must be defined before drugs can be safely used during gestation.

Page[31] defined the placental membrane as "those tissues of a developing ovum or embryo which are in contact with maternal tissues or fluids at any stage of gestation and which mediate the transfer of substances from the mother to the fetus or in the reverse direction." As we learn more about this problem, his classification of placental transport mechanisms may be useful in ordering our thinking about this subject. He used four characteristics as a basis of classification: (1) The primary physiological significance of substances being transferred, (2) the relative rates of transfer, (3) the actual or predominant mechanisms of transport, and (4) the equality or inequality of distribution of the substance.

Foulger,[12] in discussing the ability of chemicals to pass natural membranes, grouped chemical compounds into two classes:

1. Those having fairly easy access to the cell interior, such as gases; those compounds more fat-soluble than water-soluble, organic bases and unionized combinations of weak acids with weak bases; and

2. Those not able to penetrate membranes easily, such as compounds with low fat solubility, salts of organic bases and highly ionized compounds.

These two classifications are more likely to be useful in thinking about relatively short periods of exposure of the fetus to the substances, and less so when a drug is given over longer periods.

After accepting the fact that most compounds can pass rather easily from the maternal to the fetal circulation, we must then consider what happens to them once they arrive. It is a rather general opinion that the body probably does not have a specific mechanism for dealing with each new foreign compound to which it is exposed and must adapt existing mechanisms to do the job.[48] This concept of relative lack of specificity of detoxication mechanisms is not in accord with some studies of micro-organisms showing that certain bacteria can synthesize specific proteins that deal with new foreign substances. At least in humans these mechanisms are often not efficient enough to eliminate a drug with a minimum of harmful effects. The resulting chemical alteration may at times produce a

From the University of California at Los Angeles Medical Center, Los Angeles 24.

Submitted July 11, 1960.

substance more toxic than the original compound, as is the case, for example, with the detoxication of fluoroacetate.

The mechanism for eliminating undesirable substances from the body is called detoxication, the processes of which can be divided into two main phases.[48] The first is the oxidation, reduction or hydrolysis of the material, which may result in the activation of a biologically inactive compound, alteration of the substance's activity or the inactivation of active compounds. We still have very little information as to the clinical significance of this phase. The second phase is ordinarily an inactivation process with the occasional exception of what has been called "lethal synthesis." This phase consists of one of various methods of converting the compound into a product which the kidneys, or perhaps the liver, can excrete. Understanding this latter phase has become of great clinical importance to pediatricians. This phase is the conjugation of the compound with various substances such as glucuronic acid, glycine, sulfate and acetate. Conjugation with glucuronic acid has assumed major clinical significance in the past few years, and we know that the two enzymes that bring about this reaction, glucuronyl transferase and uridine diphospho glucose dehydrogenase, are present in low concentration in premature and full-term infants during the first few days of life.[7,25] The enzyme level bears a direct relation to the body's ability to excrete bilirubin and thus to the production of kernicterus in the neonatal period.

We also know that certain drugs can influence this portion of bilirubin metabolism by interfering with its conjugation with glucuronic acid or with the binding of bilirubin to serum albumin, which is a preliminary step to conjugation. Synthetic preparations of vitamin K when given in large doses to the mother have resulted in potentiation of serum hyperbilirubinemia.[1,13,18,26] This is primarily the result of increased hemolysis, probably related to an instability of blood glutathione in newborns and premature infants with subsequent leakage of potassium from the red cell. The glutathione seems necessary for maintenance of the gradient in concentration of the two sides of the cell membrane. The elevated serum bilirubin places a heavy load on the poor conjugating mechanism in these infants.

The long-acting sulfa drugs such as sulfamethoxypyridazine (Kynex®) and sulfadiamethoxine (Madribon®) can persist for days in detectable concentrations in the blood of newborn infants after administration to a mother before delivery.[30,38] This can interfere with bilirubin conjugation and excretion by displacing the bilirubin from its protein binding. The free "indirect" bilirubin can then apparently injure the extrapyramidal nuclei of the brain. Kernicterus has resulted at bilirubin levels of 12 to 15 mg. per 100 cc. in newborns who received sulfa therapy. The salicylates and phenergan can act in a manner similar to that of the sulfas, although evidence that they can have a deleterious effect when given to mothers before delivery is not available as yet. Chlorpromazine (Thorazine®) may possibly interfere with bilirubin metabolism by binding of serum albumin. It is a common drug in use for the analgesia of labor, in combination with other drugs, and will have to be evaluated for this possibility of toxicity to the fetus.

Chloramphenicol has been shown to be conjugated with glucuronic acid in the course of its elimination from the body, and in the newborn this reaction may be delayed.[9,24,46] The hydrolyzed free chloramphenicol is toxic, and has been shown to cause an increased neonatal mortality when used in dosages over 50 mg. per kilogram of body weight per day or 25 mg. in newborn infants or 25 mg. per kilogram per day in premature infants. It apparently passes the placenta poorly, which may be the reason for its seeming innocuousness when used during pregnancy.

Certain drugs have been noted to produce ill effects on the fetus when administered earlier in pregnancy. Our present criteria for recognizing such effects are very crude; but even so, we have evidence of a potent teratogenic effect of the anticancer and antileukemic drugs, and a definite effect of the antithyroid drugs as well as radioactive iodine. The masculinization of newborn girl babies by various hormones given to mothers early in pregnancy is also well documented.

Aminopterin is perhaps the best known of the drugs with teratogenic effects. Because of its pronounced toxicity to the fetus, it has been used by some physicians to induce therapeutic abortions.[32] However, some hardy fetuses have survived this therapy and have had extensive malformations at birth. Other drugs in this general class have been incriminated, and in animal experiments several have produced fetal death or malformations. Smith[37] reviewed these studies well. This effect seems to be directly related to dosage. Cortisone has been shown to produce malformations in rats when given in high dosage. There is no evidence that ill effects on the fetus have occurred in humans. Radioactive iodine has resulted in fetal death and extensive malformations. Goldstein[14] reported a case of a woman with metastatic thyroid carcinoma who had I^{131} therapy and six days later was delivered by hysterotomy of an 18 weeks old fetus. The infant was malformed and its thyroid gland was found to contain a large amount of radioactive iodine. Valensi[44] reported a woman treated for toxic goiter with I^{131} who subsequently stopped menstruating, had an unevent-

ful pregnancy and was delivered of a premature infant with extensive congenital anomalies that died shortly after birth. These instances would suggest that radioactive iodine is a dangerous drug for the fetus.

There is ample evidence that iodides and the thiouracils may produce goiter or hypothyroidism in the fetus.[6,11,27,34] From the pediatrician's point of view a little hyperthyroidism is much preferable to the attendant increased fetal mortality and incidence of malformations seen in infants born to hypothyroid mothers (that is, hypothyroidism not secondary to surgical operation). It is of interest in connection with the effect on the fetal thyroid that the thyroid tissue in the fetus does not seem to take up iodine during the first three or four months of gestation.[2,28]

Androgens, progestins and estrogens have all been incriminated as producing masculinization of female newborn infants of some mothers who had received the hormone during early gestation.[4,5,17,29,43] There has been some reluctance to accept that estrogens are a cause of this induced adrenogenital syndrome, but that the other substances are culpable is well documented. It has been shown that until after the seventh month of gestation, very little estrogen enters the fetal circulation in the normal situation. The criteria set down for a diagnosis of masculinization secondary to maternal hormone therapy are an exposure to one of these drugs during the pregnancy, a female sex chromatin pattern of the infant, normal urinary 17-ketosteroids, and no progression of the clinical manifestations.[19] These infants may have anatomic abnormalities of the external genitalia, although there are no reports of an abnormality of internal organs. One interesting case has been reported of an infant whose mother during gestation had received large doses of testosterone for 51 days early in pregnancy.[17] The infant had scrotal rugae, and urinated through the tip of a small phallus. The uterus, tubes and ovaries were normal. The sex chromatin pattern was female, and the urinary 17-ketosteroids normal.

One realizes of course that these drugs are commonly given to pregnant women and only occasionally do the foregoing manifestations occur. This suggests that there may be an abnormality of the mother's ability to metabolize progestins, androgens or estrogens respectively, or in the transmission of the hormone across the placenta.[47]

An interesting phenomenon described in the recent literature is the occurrence of withdrawal symptoms in infants born to mothers addicted to narcotics.[22,23,36,39] In such cases the mothers usually had had injections of the drug within a week of the delivery. The picture is a characteristic one: The infant is decidedly irritable, may be flushed, and has a high-pitched, constant, cerebral cry. Convulsions may occur. The mortality rate in such infants is definitely increased unless the condition is recognized and promptly treated. This diagnosis may be difficult because of attempts to conceal the addiction. Infants born to mothers addicted to alcohol may show milder symptoms suggesting a similar withdrawal syndrome.

The barbiturates are a group of drugs capable of severely depressing the fetal respiratory centers. A study of pregnant women in the fourth to the seventh month of gestation who had hysterotomy for various reasons after receiving an ordinary sedative dose of the drug showed that the concentration in fetal blood reached an equilibrium with maternal blood within as little as 30 minutes after an intramuscular injection. The elimination of the drug was as prompt with the fetus as with the mother. The transfer of pentothal after intravenous injection has been shown to occur almost immediately. Fetal blood concentration was found to be 74 per cent of that in the maternal blood level one minute after injection. This certainly makes pentothal seem worthy of great respect, although a number of reports recommend it as a good obstetrical anesthetic agent in selected cases. There has been no evidence of appreciable fetal depression when the drug was given by physicians experienced in its use.

A number of other drugs have been observed to produce undesirable effects on the fetus when given to the mother. Reserpine in 16 per cent of 77 mothers who received the drug before delivery caused considerable nasal stuffiness in the newborn infant.[8] This may result in feeding difficulties for the first few days of life and is ameliorated by decongestant nose drops administered for two or three days. Veratrine may produce fetal bradycardia. Hexamethonium may cause symptoms in the newborn identical to those of intestinal obstruction. A careful history can prevent an unnecessary operation.[45]

Dicumarol and related anticoagulant drugs may produce intracranial bleeding with possible permanent brain damage.[42] Phenobarbital, the sulfa drugs and salicylates may cause bleeding in the fetus when given to mothers during pregnancy; this in some cases has been associated with a decreased level of Stuart factor.

Tranquilizers can potentiate analgesics and increase central nervous system depression.[20] Nalline also can be a depressant, especially when given in conjunction with ether anesthesia. However, it can be lifesaving to the infant depressed from morphine or its derivatives administered during labor.

Nicotine has been said to produce premature beats in the fetus. Digitalis is relatively nontoxic and

little of a pharmacological dose passes the placental barrier; what little does pass is for the most part chemically altered and its effect greatly reduced. However, when related to concentration by weight of cardiac tissue, the fetal heart has a concentration at least equal to maternal tissue levels.[10,16]

The effects of the various anesthetic gases as depressants are well known and need no repetition here.[16]

Pharmacological studies of the antibiotics in general have shown that they pass the placenta fairly easily, although the fetal concentration is usually from one-half to two-thirds of the maternal blood concentration. There is a report of a case in which penicillin given to a mother caused severe anaphylactic shock which resulted in fetal death. This occurred in the ninth month of gestation.[21] An interesting case report which appeared in 1958 suggests that streptomycin passes the placenta and may result in deafness in the infant.[3] The child's mother in that case received the streptomycin for tuberculosis therapy.

While further investigation in the area of drug effects on the fetus continues, we must exercise great caution in the use of chemical therapy during pregnancy. We are fortunate that common drugs such as aspirin and phenobarbital have not produced more problems. Because the use of drugs during pregnancy is increasing rapidly, obstetrical and pediatric histories must include detailed reference to any therapy given, especially when complications arise in the fetus or newborn.

University of California at Los Angeles Medical Center, Los Angeles 24.

REFERENCES

1. Biskind, J. I., and Herman, I.: Vitamin K, its relationship to unexplained jaundice in the newborn, Obstet. and Gynec., 13:41, Jan. 1959.

2. Benson, R. C., et al.: Thyroid function in pregnancy, Obstet. and Gynec., 14:11, June 1959.

3. Bolletti, M., and Croatto, L.: Deafness in a five-year-old girl resulting from streptomycin therapy during pregnancy, Acta. Paediat. Lat., 11:1, 1958.

4. Bongiovanni, A. M.: Comments on estrogen induced female pseudohermaphrodism in the newborn, Year Book of Pediatrics, 375, 1958.

5. Bongiovanni, A. M., et al.: Masculinization of the female infant associated with estrogen therapy alone during gestation; four cases, J. Clin. Endocr., 19:1004, 1959.

6. Branch, L. K., and Tuthill, S. W.: Goiter in twins resulting from propylthiouracil given during pregnancy, Ann. Int. Med., 46:145, 1957.

7. Brown, B., and Zuelzer, W.: Studies on the neonatal development of the glucuronide conjugating system, J. Clin. Invest., 37:332, March 1958.

8. Budnick, I. S., et al.: Reserpine therapy during pregnancy, A.M.A. J. Dis. Child., 90:286, Sept. 1955.

9. Burns, L. E., et al.: Fatal circulatory collapse in premature infants receiving chloramphenicol, N.E.J.M., 261: 1318, Dec. 24, 1959.

10. Dimond, E.: Digitalis, Thomas, Springfield, Ill., 1957.

11. Elphinstone, N.: Thiouracil in pregnancy, Lancet, 1:1281, June 27, 1953.

12. Foulger, J. H.: Chemicals, Drugs and Health, Thomas, Springfield, Ill., 1959.

13. Gleiss, J.: Methyl-naphthochinon-Gaben and Gelbsucht bei unreifen Neugeborenen, Mschr. Kinderheilk., 106:58, 1958.

14. Goldstein: Effect of radioactive iodine therapy during pregnancy; case report, So. Afr. M. J., 1:239, 1958.

15. Goodfriend, M. J., et al.: Effects of maternal narcotic addiction on the newborn, Am. J. Obst. and Gynec., 71:29, Jan. 1956.

16. Goodman, L. S., and Gilman, A.: Pharmacological Basis of Therapeutics. Second edition.

17. Gruenwaldt, E., and Bates, T.: Non-adrenal female pseudohermaphrodism after administration of testosterone to a mother during pregnancy, Pediatrics, 20:503, 1957.

18. Haupt, H., and Krebs, H.: Ueber Wirkring and Nebenwirkungen von Vitamin K-Praeparaten bei der Anwendung im Neugeborenenalter, Z. Kinderheilk., 81:330, 1958.

19. Hillman, D. A.: Masculinization in the newborn female infant secondary to maternal hormone therapy, Canad. Assn. M. J., 80:200, 1959.

20. Hodges, R. J. H., and Bennett, J. R.: Some contraindications to the use of chlorpromazine, J. Obst. Gynec. Br. Emp., 66:91, 1959.

21. Kosim, H.: Intrauterine fetal death as a result of anaphylactic reaction to penicillin in a pregnant woman, Dapim Refuim, 18:136, 1959.

22. Krause, et al.: Heroin addiction among pregnant women and their newborn babies, Am. J. Obst. and Gynec., 75:754, April 1958.

23. Kunstadter, R. H., et al.: Narcotic withdrawal symptoms in newborn infants, J.A.M.A., 168:1008, Oct. 25, 1958.

24. Lambdin, M. A., et al.: Chloramphenicol toxicity in prematures, Pediatrics, 25:935, 1959.

25. Lucey, J. F.: Review article: Hyperbilirubinemia, Pediatrics, 25:698, April 1960.

26. Lucey, J. F., and Dolan, R. G.: Hyperbilirubinemia of newborn infants associated with the parenteral administration of a vitamin K analogue to the mothers, Pediatrics, 23:553, 1959.

27. Morris, D.: Transient hypothyroidism in a newborn infant, Lancet, 1:1284, June 27, 1953.

28. Myant, N. B.: Passage of thyroxine and triiodothyronine from mother to foetus in pregnant women, Clin. Sci., 17:75, 1958.

29. Nellhaus, G.: Artificially induced pseudohermaphroditism, N.E.J.M., 258:935, May 8, 1958.

30. Odell, G. B.: Dissociation of bilirubin from albumin, J. Pediat., 55:268, 1959.

31. Page, E. W.: Transfer of materials across the human placenta, Am. J. Obstet. and Gynec., 74:705, Oct. 1957.

32. Petersohn, K.: Aminopterin, ein oral wirksamer abortivum?, Med. Klin., Berlin, 53:1405, Aug. 15, 1958.

33. Ploman, L., and Persson, B. H.: On the transfer of barbiturates to the human fetus and their accumulation in some of its vital organs, J. Obst. and Gynec. Br. Emp., 64: 706, 1957.

34. Riley, I. D., and Sclare, G.: Thyroid disorders in the newborn, Brit. M. J., 5025:979, April 27, 1957.

35. Rogers, J. B., et al.: Placental alterations in toxemia of pregnancy in guinea pigs, Lab. Invest., 7:614, 1958.

36. Schneck, J.: Narcotic withdrawal symptoms in newborn infant resulting from maternal addiction, Pediat., 52:584, May 1958.

37. Smith, R. B. W.: Hodgkins disease and pregnancy, A.M.A. Arch. Int. Med., 102:777, 1958.

38. Sparr, R. A., and Pritchard, J. A.: Maternal and newborn distribution and excretion of Kynex, Obst. and Gynec., 12:131, Aug. 1958.

39. Steg, N.: Narcotic withdrawal reaction in the newborn, A.M.A. J. Dis. Child., 94:286, Sept. 1957.

40. Taylor, E. S.: Effect on fetus of various drugs given during pregnancy, Am. J. Obst. and Gynec., 74:716, Oct. 1957.

41. Thiersch, J. B.: Therapeutic abortion with a folic acid antagonist, 4-aminopteroyl glutamic acid administered by the oral route, Am. J. Obst. and Gynec., 63:1298, 1952.

42. Toulouse, R., et al.: Accidents hemorragiques chez des nouveau-nes dont les meres ont eu un traitement anticoagulant au cours de la grossesse, Rev. Franc. Gynec., 54: 203, 1959.

43. Uhlig, H.: Fehlbildungen nach Follikelhormonen beim Menschen, Geburtsh. u. Frauenheilk., 19:346, 1959.

44. Valensi, G., and Nahum, A.: Effect on fetus of radioactive iodine given during gestation, Tunisie Med., 36:69, 1958.

45. Von Bruecke, F. v.: Schadegungen der Frucht durch Artznermittelgebrauch der Mütter, Munch. Med. Wschr., 100:560, April 11, 1958.

46. Weiss, C. F., et al.: Chloramphenicol in the newborn infant: A physiologic explanation of its toxicity when given in excessive doses, N.E.J.M., 262:793, April 21, 1960.

47. Wilkins, L., et al.: Masculinization of the female fetus associated with administration of oral and intramuscular progestins during gestation: Non-adrenal female pseudohemaphrodism, J. Clin. Endocr., 18:559, June 1958.

48. Williams, R. T.: Detoxication Mechanisms, John Wiley and Sons, New York, Second Edition, 1959.